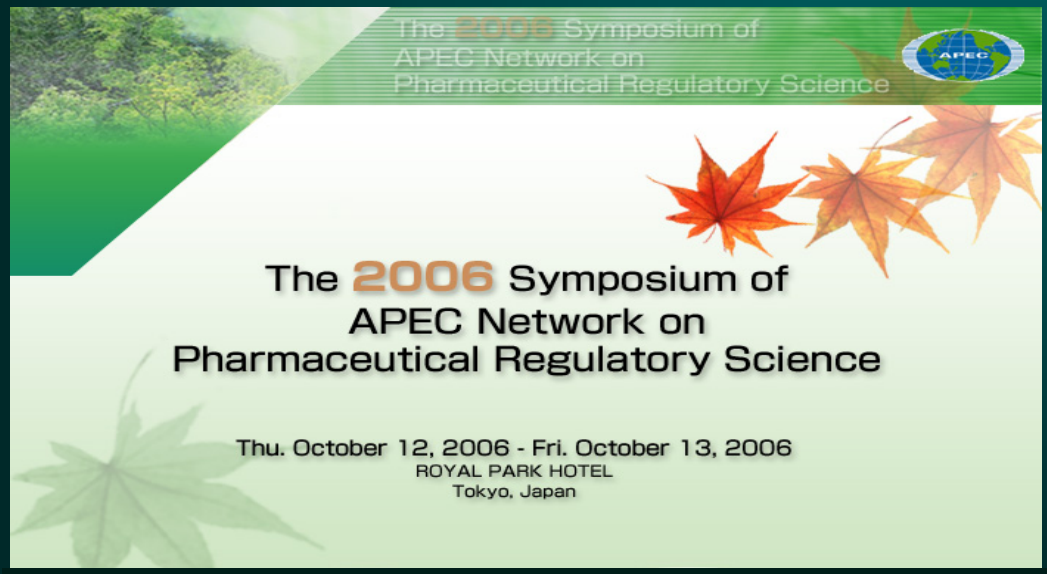
Combination Products



M. Gropp; Abbott Vascular, Brussels

Caveats

- Complex topics
- Focus mostly on device-drug combinations, but similar considerations apply to other combination products
  - Taken from medical device perspective
- Personal views

Building a Prosperous Asia-Pacific through Free and Open Trade and Investment

Promoting the Safe and Efficient Movement of Goods, Services and People through the Asia-Pacific Region

Source: *About APEC*, APEC Secretariat, 2004

to clothes to communications.

Highlights include -

- APEC economies have improved their governance and are ahead of the rest of the world in this area.
- APEC's Economic and Technical Cooperation is contributing to the reform process.
- The APEC region is meeting the Millennium Development Goals.

Extending the Benefits of the Knowledge-Based Economy to the People of the Asia-Pacific

Source: *APEC At a Glance*, APEC Secretariat, 2006

What is a “medical device”?

What is a “medical device”?

USA definition:

“… an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is —

(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,

(2) **intended for use** in the **diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease**, **in man** or other animals, or

(3) **intended to affect the structure or any function of the body** of man or other animals, …

Source: 21 U.S.C. 201(h)

What is a “medical device”?

USA definition (continued)**:**

“… and which **does not achieve its primary intended purposes through chemical action** within or on the body of man or other animals and which is **not dependent upon being metabolized for the achievement of its primary intended purposes.**” [Emphasis added]

Source: 21 U.S.C. 201(h)

What is a “medical device”?

European Union definition:

“… any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application **intended** by the manufacturer to be used for human beings for the purpose of:

- **diagnosis, prevention, monitoring, treatment or alleviation** of disease,
- **diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap**,
- **investigation, replacement or modification of the anatomy or of a physiological process**,
- control of conception, …

Source: Council Directive 93/42/EEC of 14 June 1993 concerning medical devices

What is a “medical device”?

European Union definition (continued):

“… and which **does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means**, but **which may be assisted in its function by such means**” [Emphasis added]

Source: Council Directive 93/42/EEC of 14 June 1993 concerning medical devices

What is a “medical device”?

Japan definition:

(定義) 第2条

4. この法律で「医療機器」とは、人若しくは動物の疾病の診断、治療若しくは予防に 使用されること、又は人若しくは動物の身体の構造若しくは機能に影響を及ぼすこと が目的とされている機械器具等であって、政令で定めるものをいう。

“equipments, instruments etc. specified by the government ordinance which are **intended** for use in the **diagnosis, treatment or prevention of disease in humans or animals, or intended to affect the structure and functions** of the human or animal body” [Emphasis added]

Source: The Pharmaceutical Affairs Law; Law No. 145, dated Aug. 10, 1960, as amended by Law No. 73, dated June 11, 2003

What is a “medical device”?

Global Harmonization Task Force (GHTF) definition:

“… any instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or other similar or related article:

a) **intended** by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of:

- **Diagnosis, prevention, monitoring, treatment or alleviation** of disease
- **Diagnosis, monitoring, treatment, alleviation** of or compensation for an injury,
- **Investigation, replacement, modification, or support of the anatomy or of a physiological process** …”

Source: GHTF/SG1/N29R16:2005; Information Document Concerning the Definition of the Term “Medical Device”

What is a “medical device”?

GHTF definition (continued):

- supporting or sustaining life
- control of conception,
- disinfection of medical devices,
- providing information for medical or diagnostic purposes by means of *in vitro* examination of specimens derived from the human body

and

b) which **does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means**” [Emphasis added]

Source: GHTF/SG1/N29R16:2005; Information Document Concerning the Definition of the Term “Medical Device”

What is a “medical device”?

Source: US FDA CDRH 2005 Strategic Plan

C·D·R·H Center for Devices and Radiological Health

What is a “medical device”?

- Medical devices distinguished from drugs and biological products on basis of intended mode(s) of action
  - Not metabolic, pharmacologic, or immunologic
  - May be assisted by such means
- Internationally harmonised definition exists
  - Not yet uniformly adopted
  - Opportunity for international harmonisation
- No international definition of products that may cross borderlines
  - Opportunity for international harmonisation

Drugs and medical devices differ

Drugs

- Discovered
- Stable formulation developed
- Highly mechanised manufacture
- Consumed by use
- Systemic toxicity
- Large populations of exposure
- Patient may choose to stop use

Medical devices

- Designed
- Constant iterative improvements or changes
- Often manufactured by hand operations
- Available for study after use
- Adverse events most often local in nature
- Relatively limited populations of exposure
- Generally not subject to ethnic differences
- Most intended for professional use

Source: S. Alpert, M.D., PhD. (Medtronic Corp.); Asian Harmonization Working Party, Seoul, Sept. 2006 (adapted)

Drugs and medical devices differ

Drugs

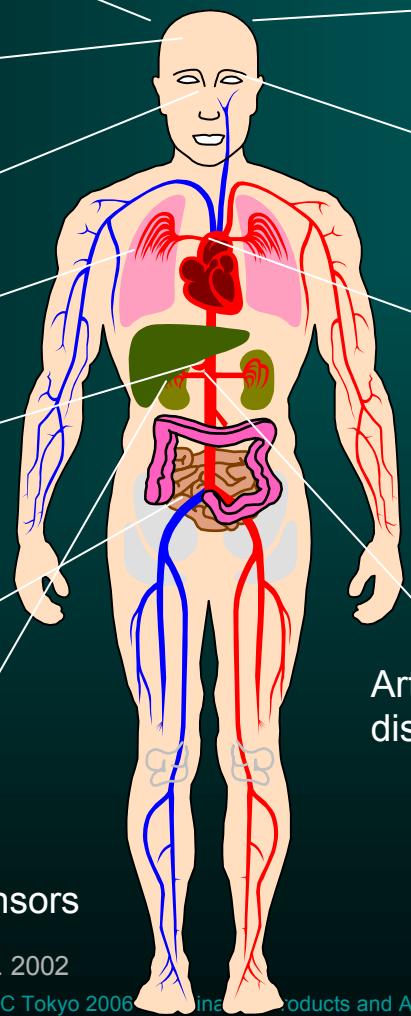
- Pure molecules
- Toxicology
- Short half-life in body
- Long market life
- Drug interactions
- Wrong drug/dose
- Clinically studied
- Good Manufacturing practice (cGMP)

Medical devices

- Complex components and assemblages
- Biocompatibility
- Durable
- Rapid product cycles
- Device malfunction
- Use error
- Often bench studied
- Quality management systems (ISO 9000 → ISO 13485)

Source: D. Schultz, US FDA CDRH; Development of New Technology and Challenges to Regulatory Harmonization; APEC 2005, Taipei, Nov. 2005 (adapted)

Addressing unmet clinical needs



Neuroprosthesis – cochlear implant

Deep brain stimulation – Parkinson's, tremor

Microsurgical implant - glaucoma

Neuroprosthesis – retinal stimulation

Sleep apnea devices

Advanced catheter technology – Alzheimer's

Interventional pulmonology - emphysema

Stomach implants - obesity

Neurostimulation - pain

-Incontinence

-obesity

Artificial pancreas, glucose sensors

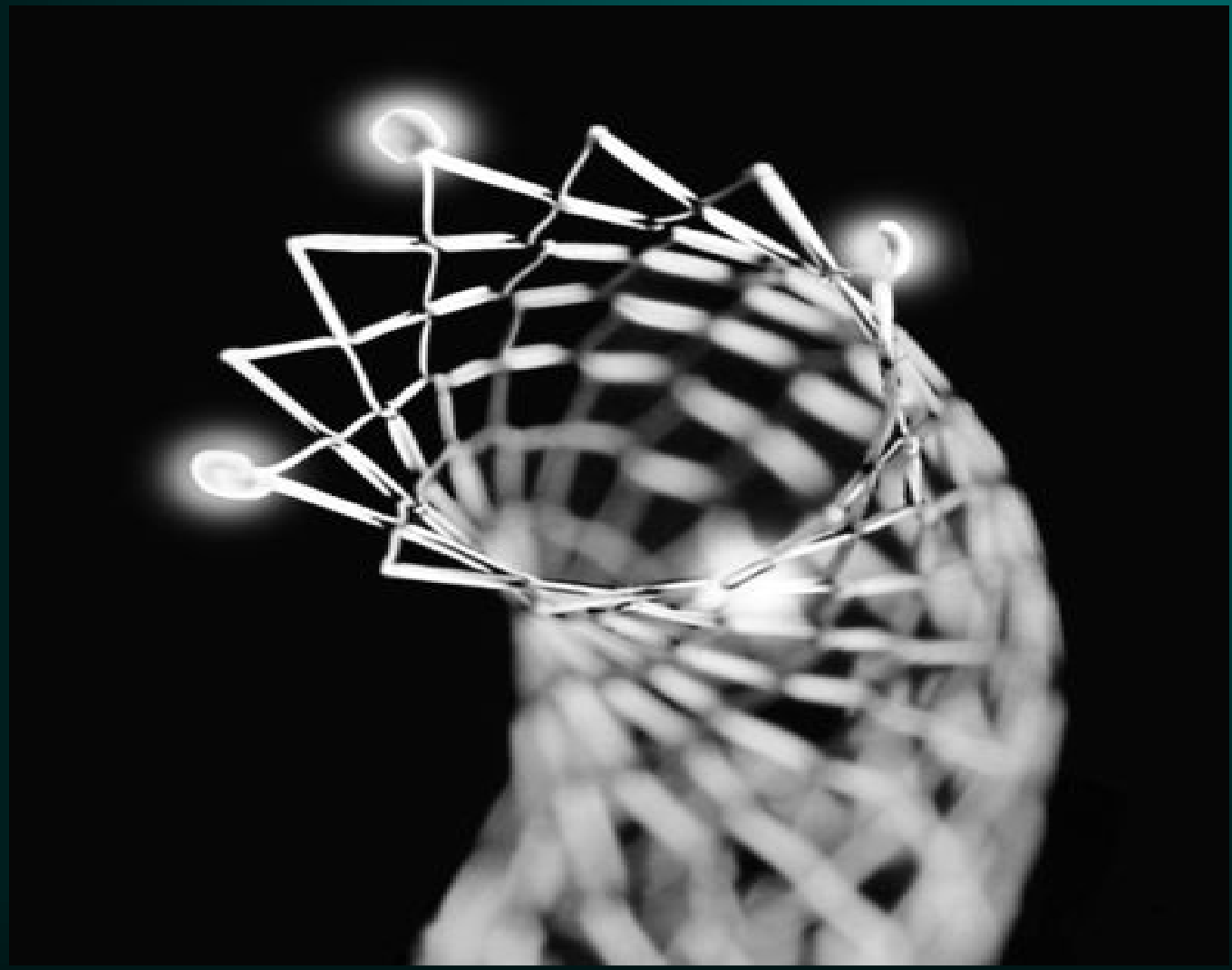
Artificial spine disc

- Percutaneous valve repair
- VADs
- Diastolic Limiters
- Ventricular sourcing
- Atrial appendage plug
- AF devices, ablation

- Tissue engineering
- RF ablation – oncology
- Minimally invasive, transcervical, permanent contraception
- Intravascular temperature mgmt for AMI, stroke

Source: Guidant Corporation; Oct. 2002

What is a “medical device”?



Source: Eucomed (modified)

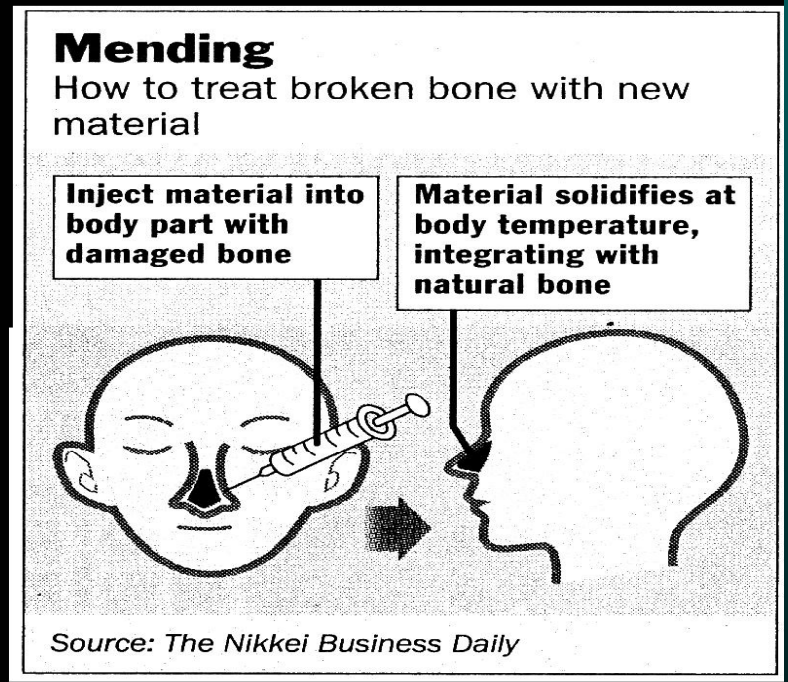
What is a “medical device”?

Injectable liquid bone substitute solidifies at body temperature

A bone substitute material that remains liquid at room temperature but solidifies at body temperature has been developed by a team of researchers at the Nara Institute of Science and Technology.

The landmark material solidifies to become part of a bone after being injected into the body while it is a liquid, opening the prospect of treating damaged bones without performing surgery. It can also be used as a kind of cement when artificial joints are affixed to bones.

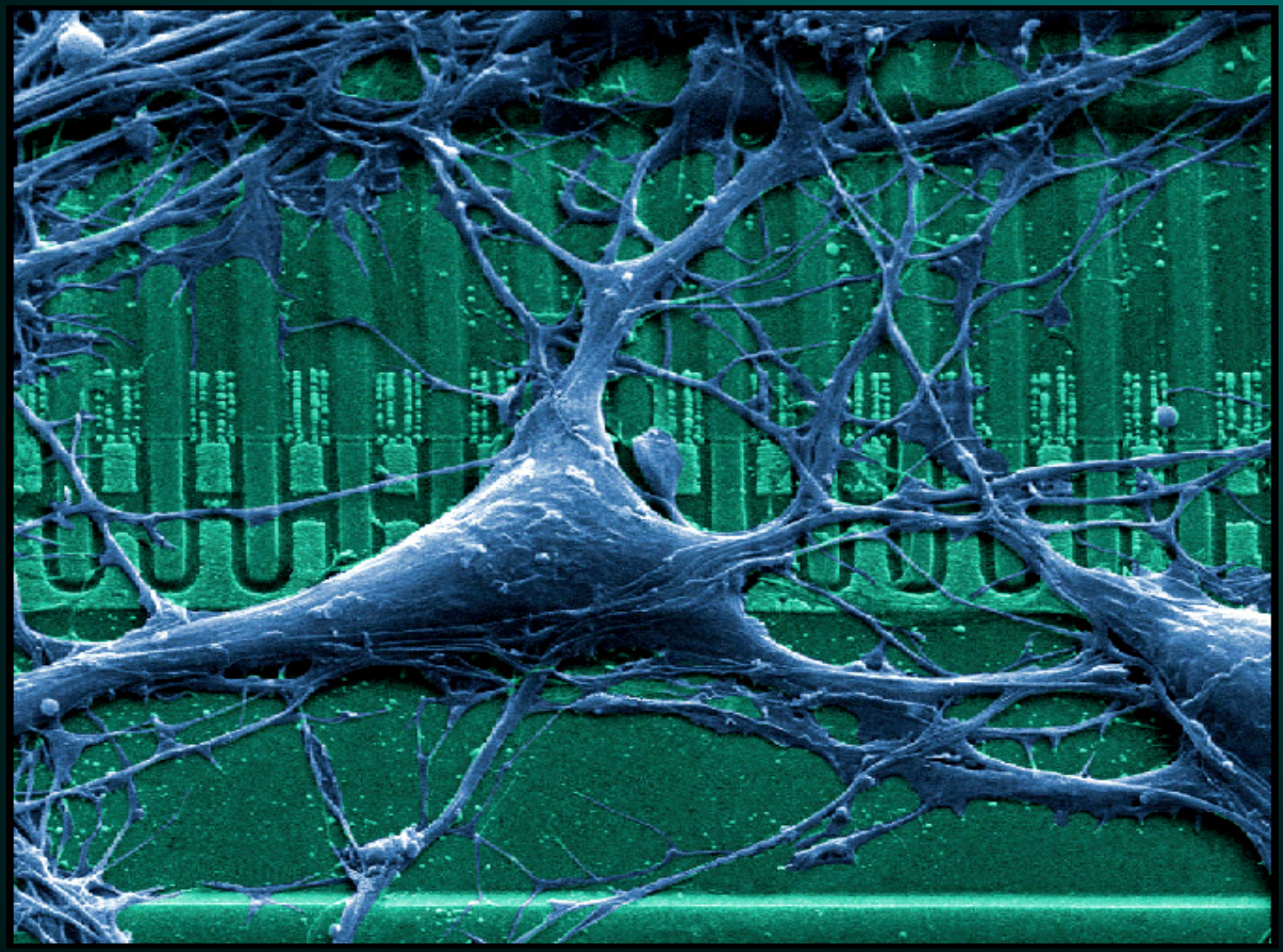
Led by Masao Tanihara, a professor of biocompatible materials science at the institute, the team was able to create the new material by combining Poly-N-isopropyl acrylamide, a type of resin that is highly sensitive to changes in temperature, with calcium phosphate, a natural substance found in bones.



The group found that the material quickly solidifies when the temperature is raised to over 33 C (91.4 F).

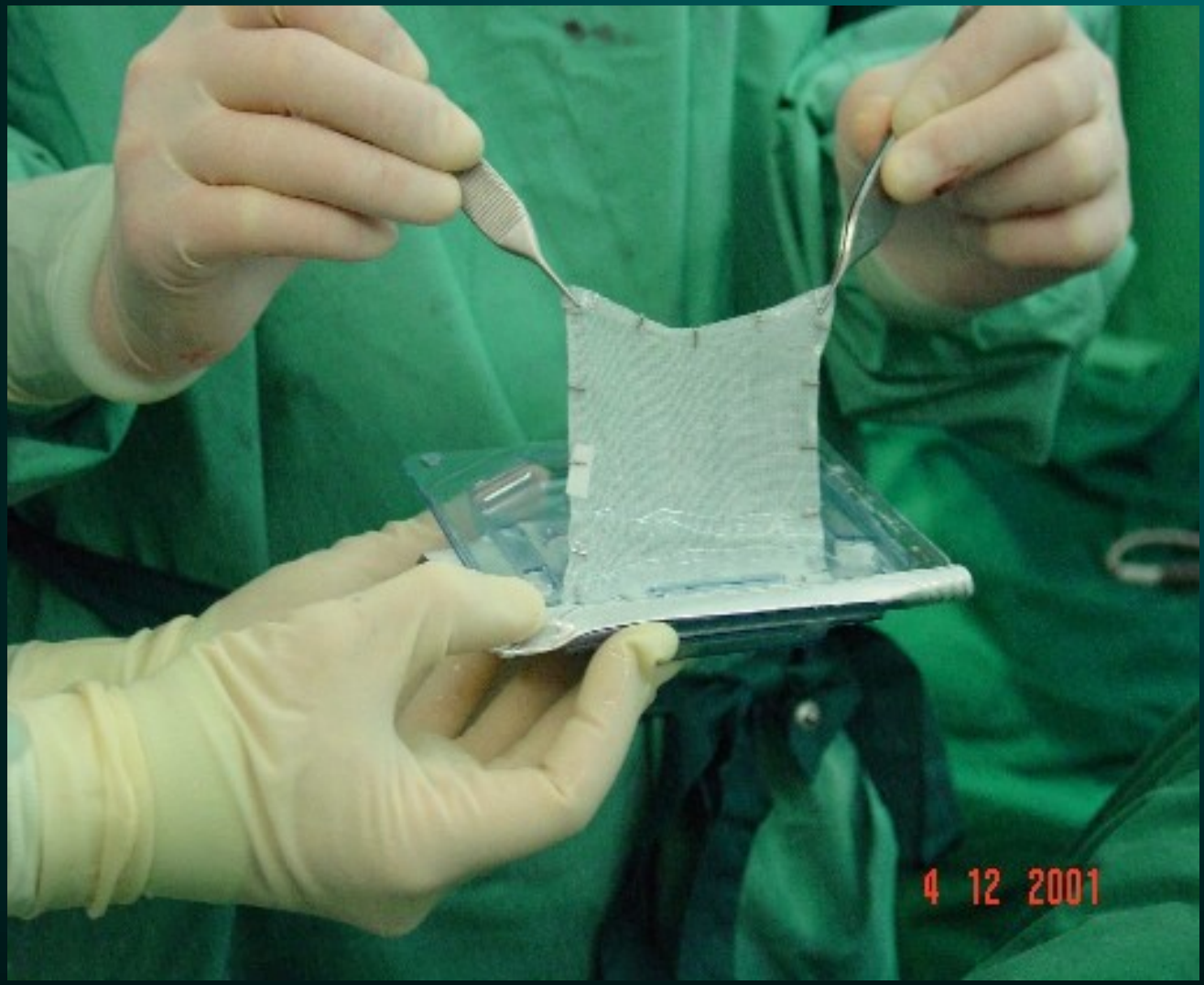
Source: Nikkei Weekly 20 Feb. 2006

What is a “medical device”?



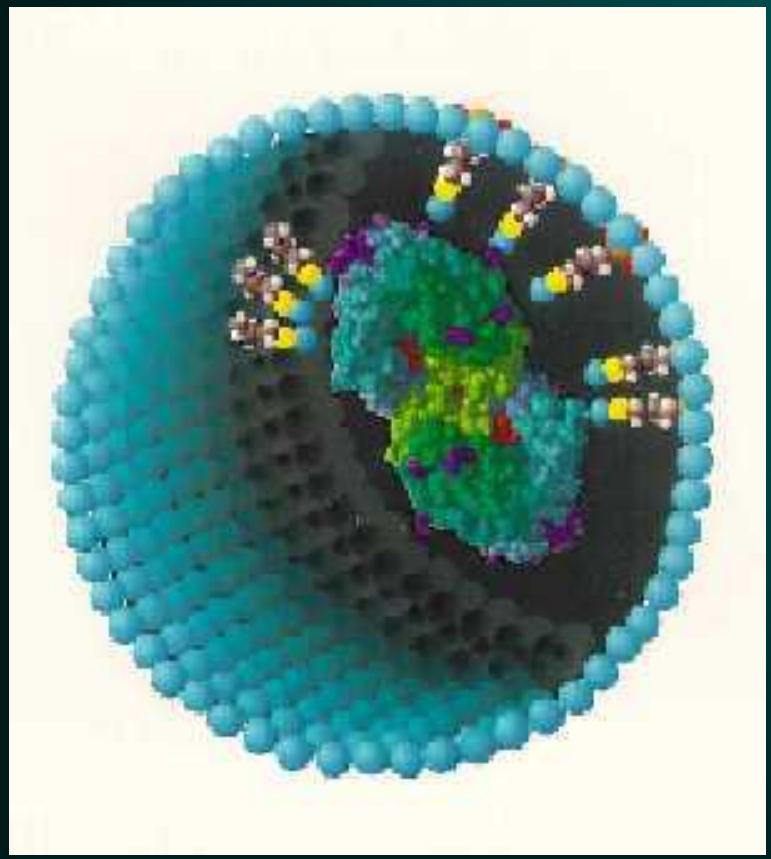
Source: Eucomed (modified)

What is a “medical device”?



Source: Eucomed (modified)

What is a “medical device”?

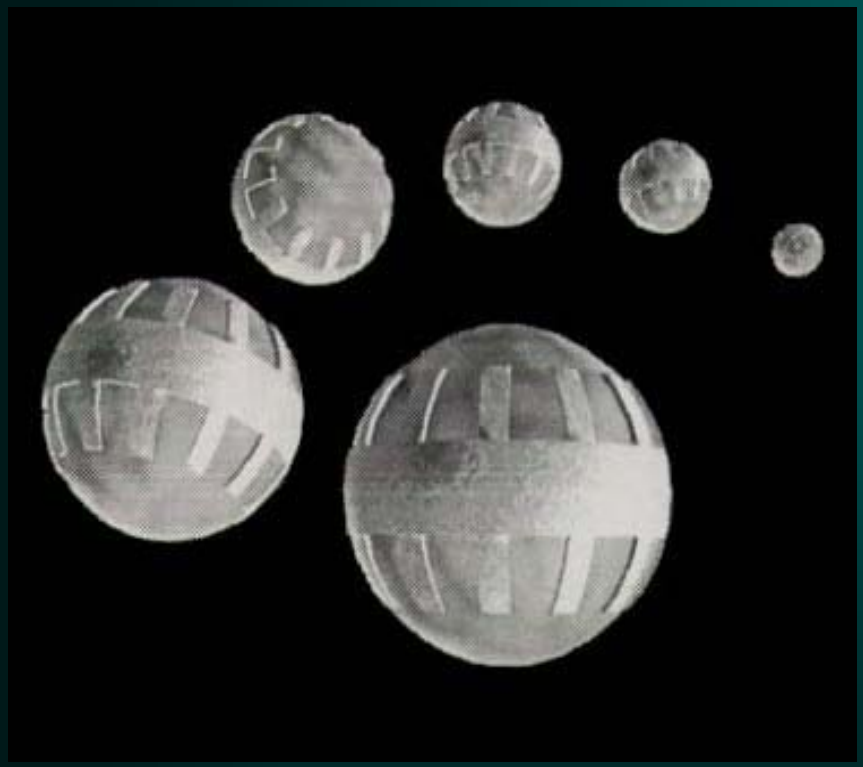


A major application of nanotechnology may be the targeted delivery of drugs to specific organs or tissues, e.g. for the treatment of cancers at their site rather than the use of systemic and often highly toxic chemotherapy

Another possible application could be the delivery to specific sites of coated nanoparticles that could then be heated using intense light thereby destroying diseased tissue and cells

Source: Eucomed (modified)

What is a “medical device”?



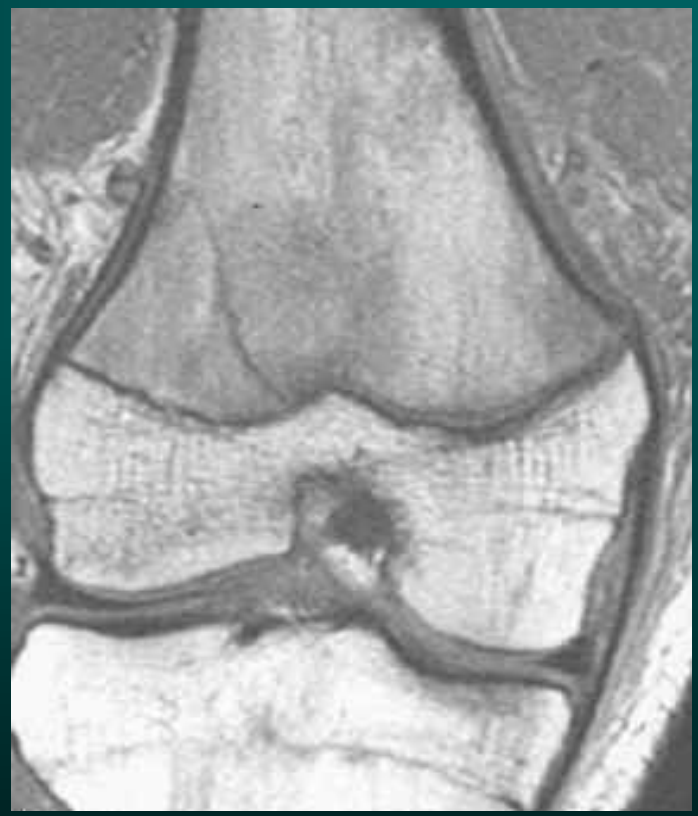
Some researchers postulate that synthetic “respirocytes” could augment oxygen supply to poorly vascularised tissues

Measuring 1 micron in diameter, it has been suggested that these could pump 236 times more oxygen to tissue than a red blood cell

They could also include an onboard nanocomputer and chemical and pressure sensors

Source: Eucomed (modified)

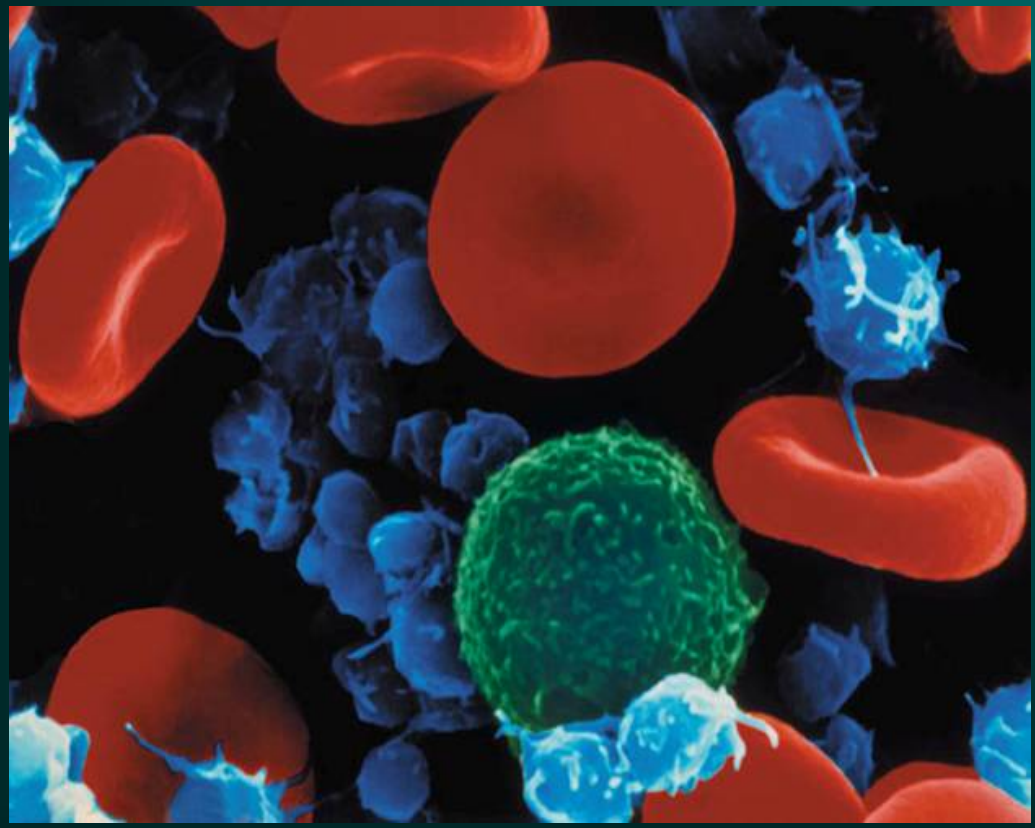
What is a “medical device”?



An example of human tissue-engineered cartilage intended to replace damaged cartilage as shown in the radiographic image

Source: Eucomed (modified)

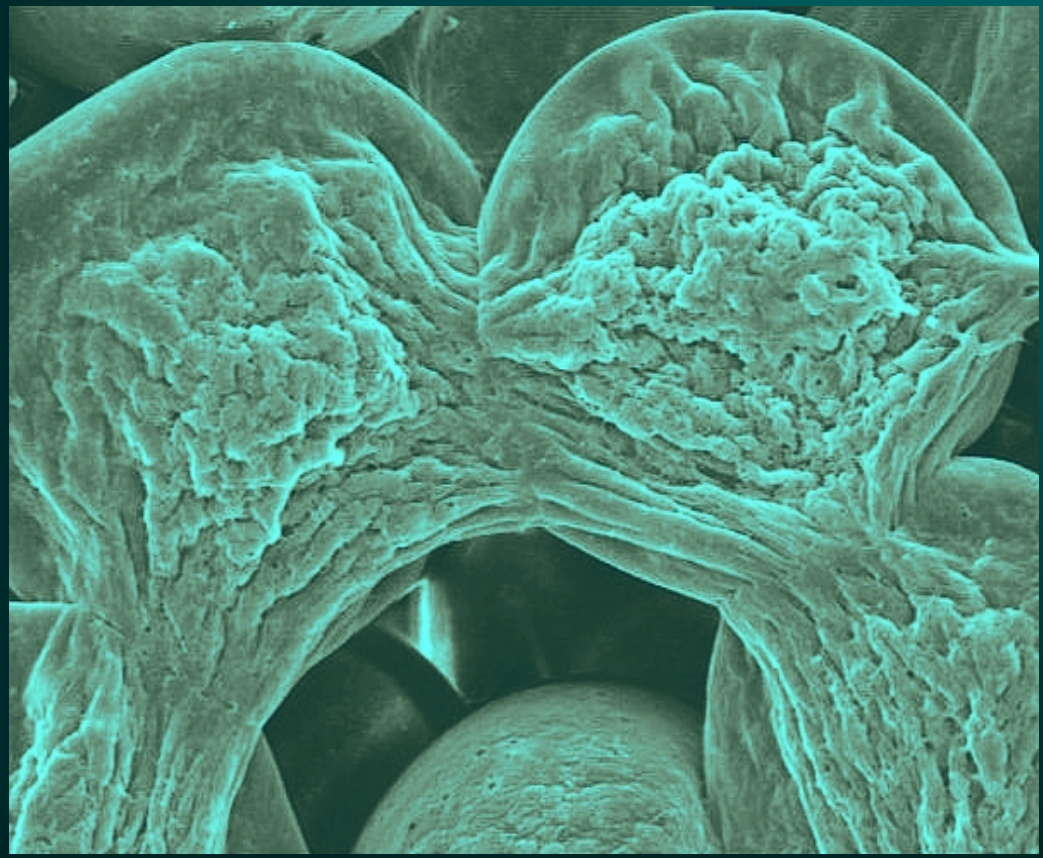
What is a “medical device”?



It is now becoming feasible to inject nano-encapsulated drugs, or metallic or semi-metallic particles, into the T-lymphocyte which can be subsequently transported to a tumour site and there released or activated physically by an external source

Source: Eucomed (modified)

What is a “medical device”?



Osteocytes growing on a spherical biopolymer scaffold (bottom of micrograph). Such products could typically be used in orthopaedic and reconstructive surgery

Source: Eucomed (modified)

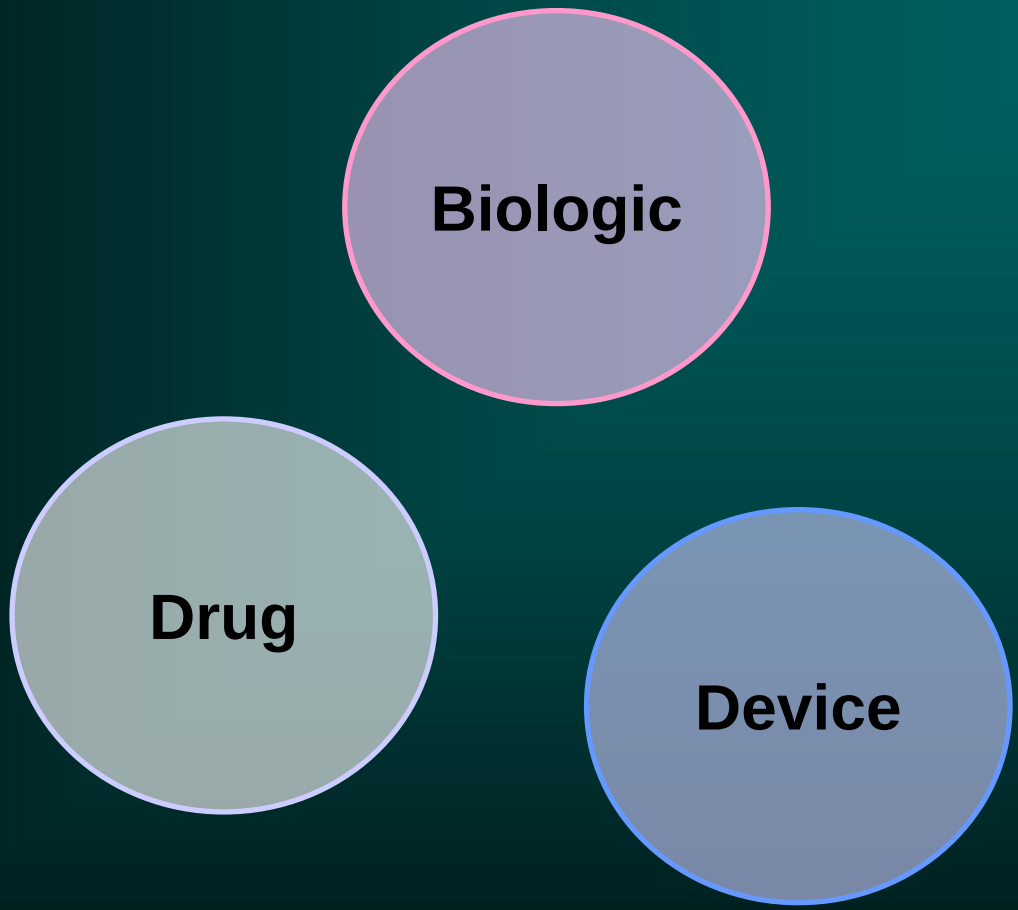
Combination products

Japan METIS (Medical Engineering Technology Industrial Strategy Consortium)

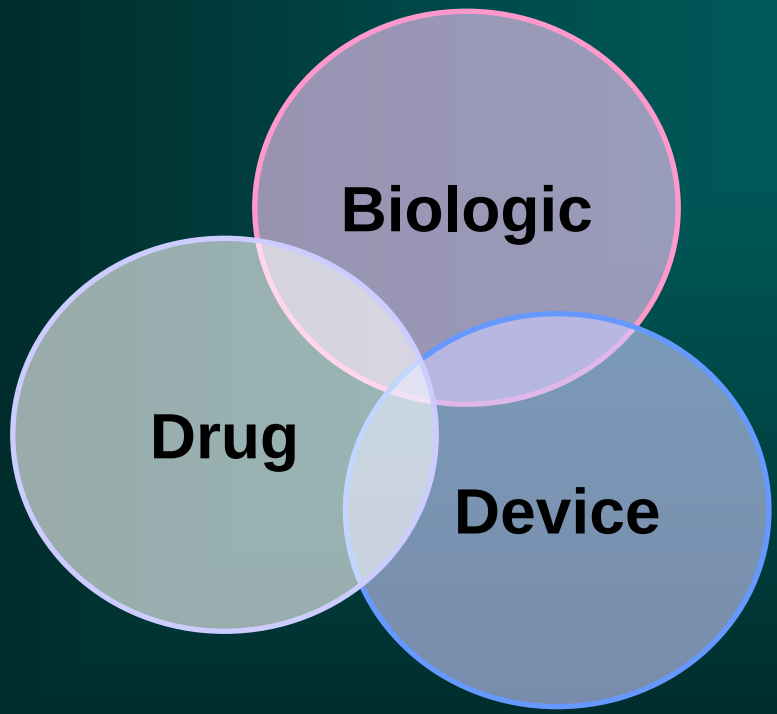
- Gene chips for diagnosis
- Diagnosis and treatment with molecular imaging
- DDS and target treatment
- Minimally invasive treatment devices
- Bionics medical equipment
- Organ function assist device
- Regenerative medical techniques for bone, cartilage, blood vessels, and cardiac muscles

Source: Japan METIS; 5 Oct. 2005

Converging medical technologies



Converging medical technologies



What is a “combination product”?

Combinations of different types of regulated products

- Drug – medical device
- Medical device – biologic
- Drug – biologic
- Drug – medical device – biologic

Combination products may be:

- Physically or chemically combined (e.g., transdermal drug delivery)
- Co-packaged in a kit
- Separate, cross-labeled products (e.g., implantable pumps)

Source: D. Schultz, US FDA CDRH; Development of New Technology and Challenges to Regulatory Harmonization; APEC 2005, Taipei, Nov. 2005

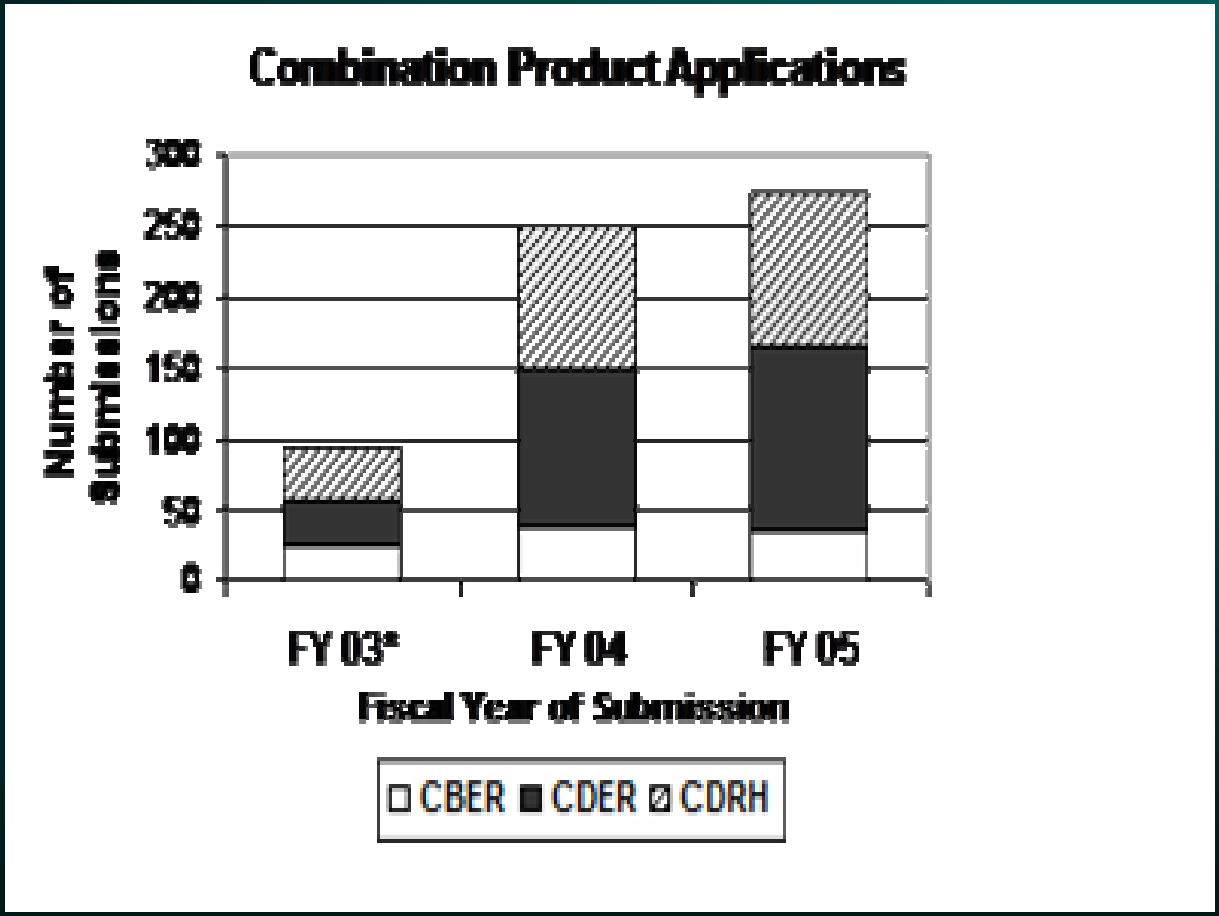
Combination products

- One item composed of two or more products that are subject to different regulatory regimes
- Two or more differently regulated items that must be used together to achieve the intended outcome
  - Often, but not always, packaged together
  - Labelled for required use together
- Often offer unique therapeutic advantages
- A regulatory challenge for regulators and industry

Source: S. Alpert, M.D., PhD. (Medtronic Corp.); Asian Harmonization Working Party, Seoul, Sept. 2006, and US FDA (adapted)

Combination products becoming more common

Combination product applications US FDA



Source: FY 2005 Performance Report to Congress; US FDA Office of Combination Products

What is a "combination product"?

- "A product comprised of two or more regulated components … that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
- Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
- A drug, device, or biological product packaged separately that according to its … labeling is intended for use only with an … individually specified, drug, device or biological product where both are required to achieve the intended use, indication, or effect …."

Source: US FDA; 21 CFR § 3.2(e)

Combination products

- In many economies, regulatory controls and requirements for drugs, devices, and biological product are similar, but different
  - One approach does not suit all products
- Pre- and post-market requirements differ
- No special type of marketing application for combination products
- Several regulatory authorities or components may have interest and expertise
- Need clear rules for determining regulatory responsibility

Combination products regulatory considerations

- How, and by whom, product will be used
- Additive effects of other components
- Entire life cycle of product should be considered
- Product's most important therapeutic benefit helps determine how to regulate

Combination products regulatory considerations

- **Mode of action:** "… the means by which a product achieves an intended therapeutic effect or action. …

  "therapeutic" action or effect includes any effect or action of the combination product intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the structure of any function of the body"

Source: US FDA; 21 CFR 3.2 (k)

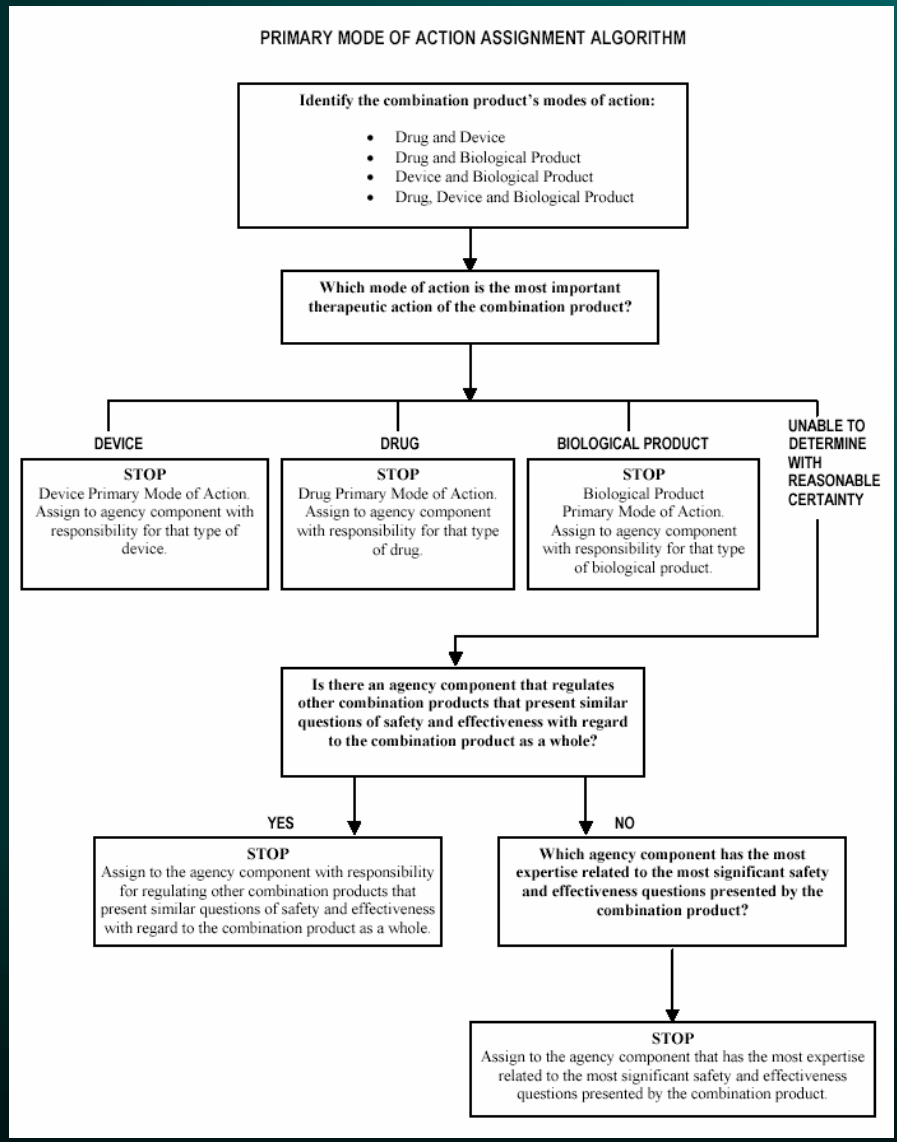
Combination products regulatory considerations

- **Primary mode of action:** "… the single mode of action of a combination product that provides the most important therapeutic action of the combination product.

  The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product"

Source: US FDA; 21 CFR 3.2 (m)

Determining “primary mode of action”



Source: US FDA Talk Paper, May 6, 2004 regarding proposed rule on combination products (http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01288.html)

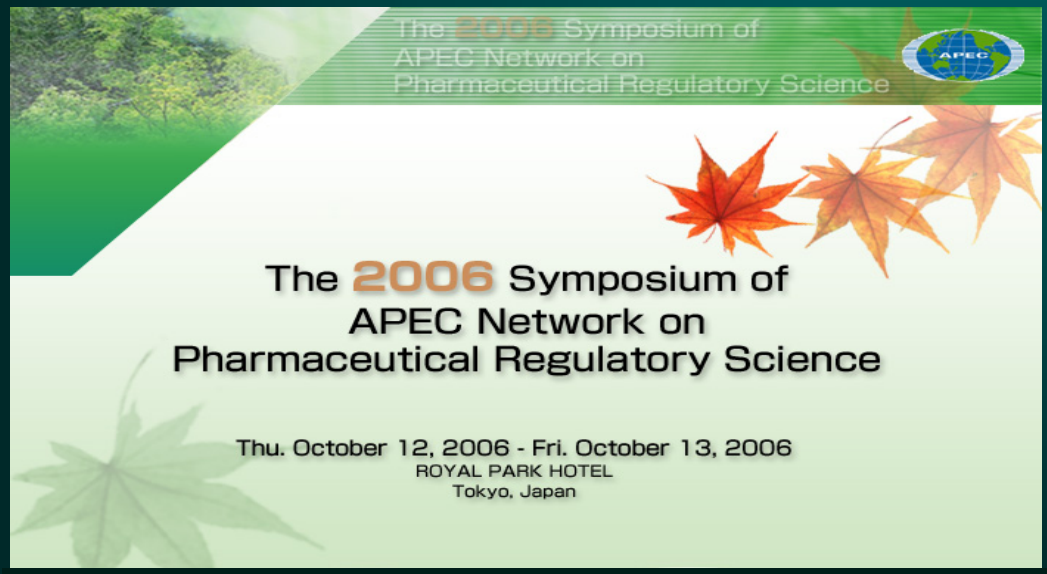
Combination products regulatory objectives

- Effective regulation of the combination – taking into account each contributing attribute
- Risk-based and proportionate controls
  - Protect patients
  - Promote innovation
- Scientifically appropriate assessments
- Avoid repetitive or unnecessary reviews
- Transparency of jurisdiction determinations, requirements and review pathways
- Timely access of patients and clinicians to these important products

Combination products -- Summary

- Combination products offer therapeutic benefits
- Combination products pose challenges for regulators and industry
- Regulatory differences derive from underlying product differences
- Regulatory requirements and authorisation pathways should be consistent and predictable
- Opportunity for international regulatory harmonisation
- Important challenge for global product development and clinical trials

Asia Regional Medical Device Regulatory Harmonization



M. Gropp; Abbott Vascular, Brussels

Caveats

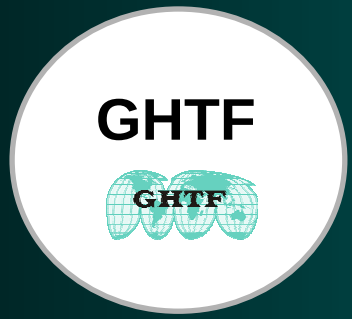
- Complex topic
- General overview

What is regulatory “harmonization”?

- Progressive convergence over time of regulatory requirements and practices
- Progressive elimination or reduction of technical differences in regulatory requirements

► Facilitates global product development and clinical investigations

International medical device regional regulatory harmonization initiatives



Global Harmonization Task Force (GHTF) History

- Informal grouping of medical device regulators and industry
- Began in 1992
- Canada, European Union, Japan, USA
  - Australia joined in 1993
  - "Founding Members"
  - Other interested countries are "Participating Members"
- Analogous to International Conference on Harmonization (ICH) in pharmaceutical sector

GHTF

Purpose:

"…. to encourage convergence in regulatory practices related to ensuring the safety, effectiveness / performance and quality of medical devices, promoting technological innovation and facilitating international trade …"

Source: GHTF

GHTF

Purpose (cont'd):

"…. the primary way in which this is accomplished is via the publication and dissemination of harmonized guidance documents on basic regulatory practices.

These documents can then be adopted / implemented by member national regulatory authorities ..."

- GHTF guidance substantially adopted in Australia, Canada, EU, and Japan

Source: GHTF

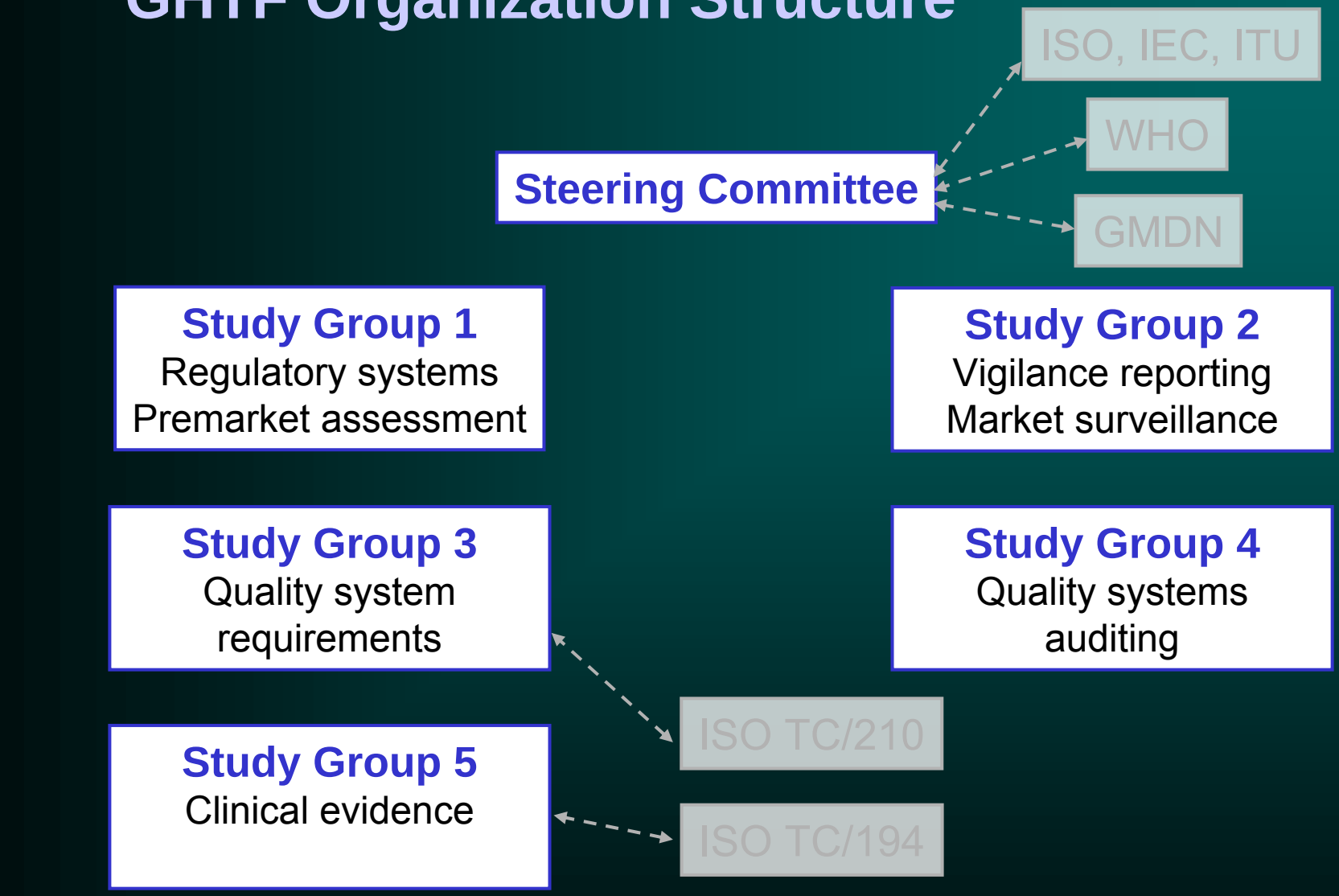
GHTF

Purpose (cont'd):

"…. GHTF also serves as an information exchange forum through which countries with medical device regulatory systems under development can benefit from the experience of those with existing systems and/or pattern their practices upon those of GHTF founding members."

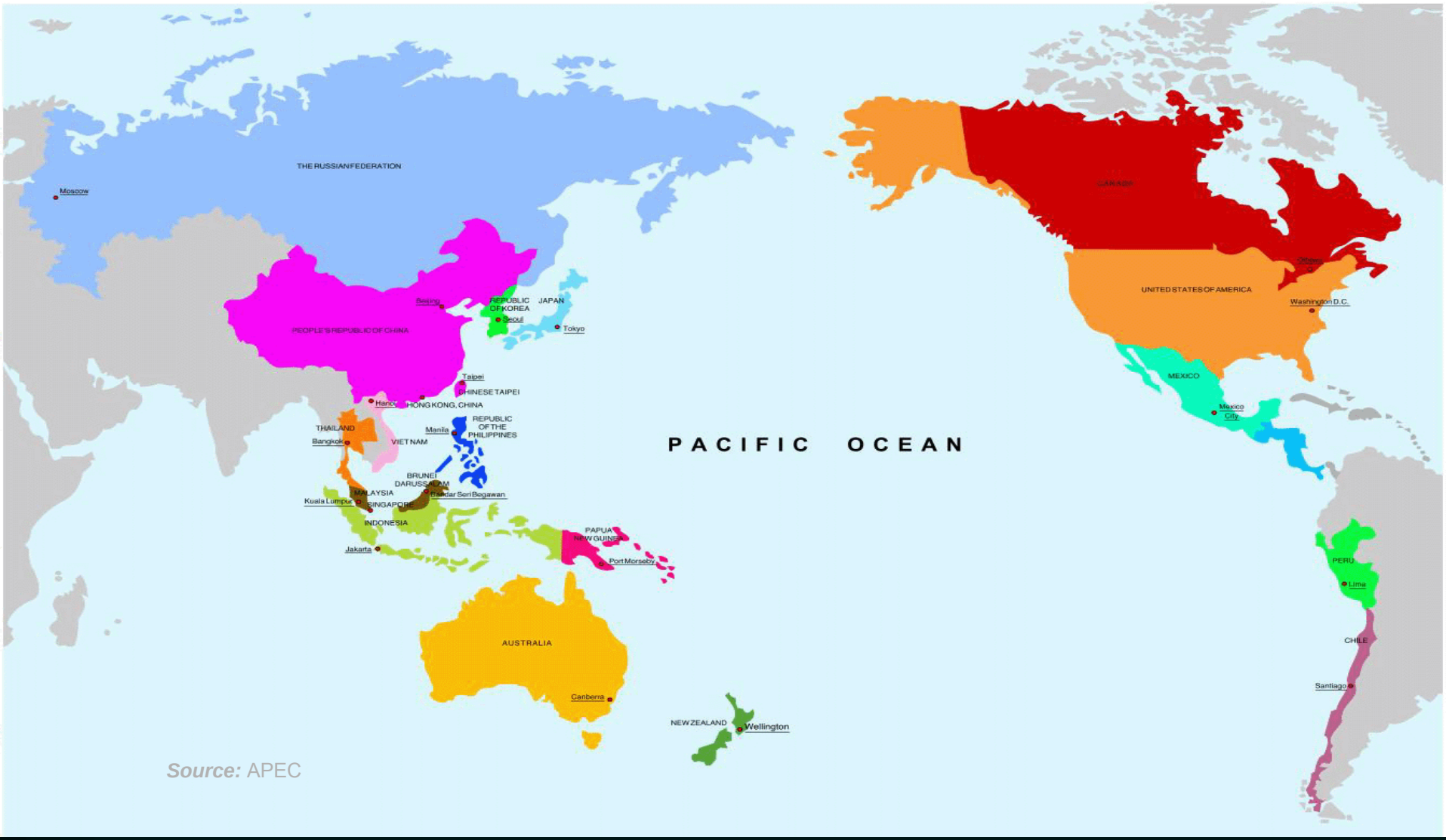
Source: GHTF

GHTF Organization Structure



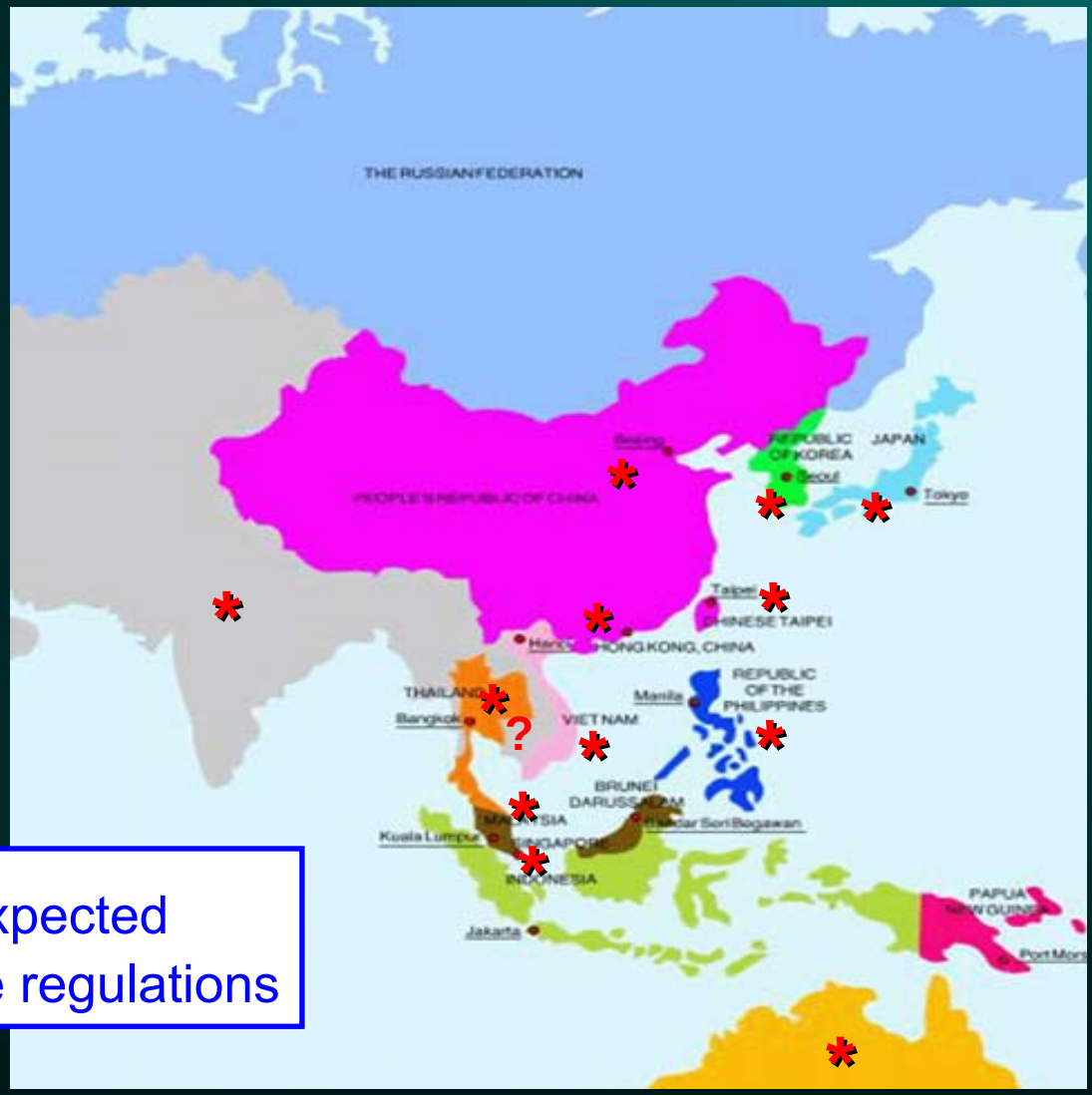
GHTF guidance documents

APEC MEMBER ECONOMIES



Source: APEC

Asia: Emerging medical technology regulation



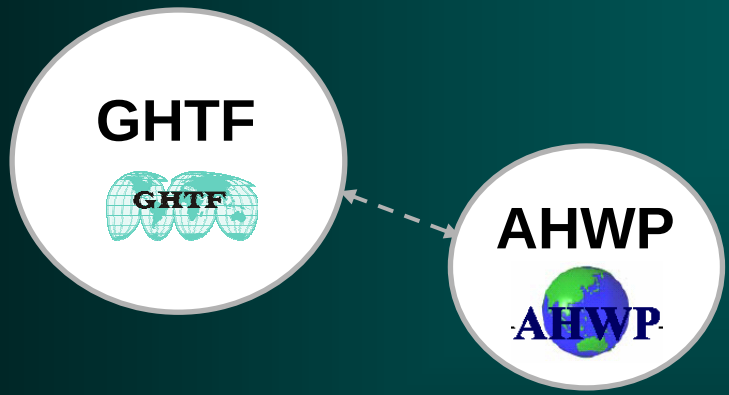
* Current or expected medical device regulations

Forces driving medical device regulation in Asia-Pacific region

- Policy objective to protect public health
- Rising public expectations of access to health care
- Rising domestic industry
- Control of trade (import and export)
- Concerns about used/second-hand equipment being placed on local market
- Lending institution interests

► Opportunity for prospective, rather than retrospective, harmonisation?

Asia-Pacific medical device regional regulatory harmonization initiatives



Asian Harmonization Working Party (AHWP)

- Formed in 1996-7
- Informal grouping
- Regional economy regulators and industry representatives

Asian Harmonization Working Party (AHWP)

Member economies (regulators and industry)

- Brunei Darussalam
- People's Republic of China
- Hong Kong SAR
- Indonesia
- Korea
- Malaysia (Chair – Ministry of Health)
- Philippines
- Saudi Arabia
- Singapore
- Chinese Taipei
- Thailand
- Vietnam

Asian Harmonization Working Party

Purpose:

"... To study and recommend ways to harmonize regulation in the Asian region with global trends and to work in coordination with the Global Harmonization Task Force and APEC. ...

Source: AHWP Terms of Reference

Asian Harmonization Working Party

Purpose:

"... The AHWP will strive to:

Examine the use of quality system requirements around the world and prospects for adopting a quality system standard based on internationally recognized and accepted quality system standard for medical devices. ..."

Source: AHWP Terms of Reference

Asian Harmonization Working Party

Purpose (cont'd):

"... Work toward building a common regulatory consensus based on acceptance of international standards as the chief means of ensuring product safety and assurance.

Move toward recognition of a common audit that can be accepted throughout the Asian region. ..."

"... Work toward a harmonized system of medical device vigilance reporting for adoption within the region and information sharing.

Source: AHWP Terms of Reference

Asian Harmonization Working Party

Purpose (cont'd)**:**

"Work with the GHTF on technical harmonization efforts and seek representation as observers at their study groups. ..."

"... Facilitate the process of regional implementation of APEC initiatives for the medical devices and equipment sector."

Source: AHWP Terms of Reference

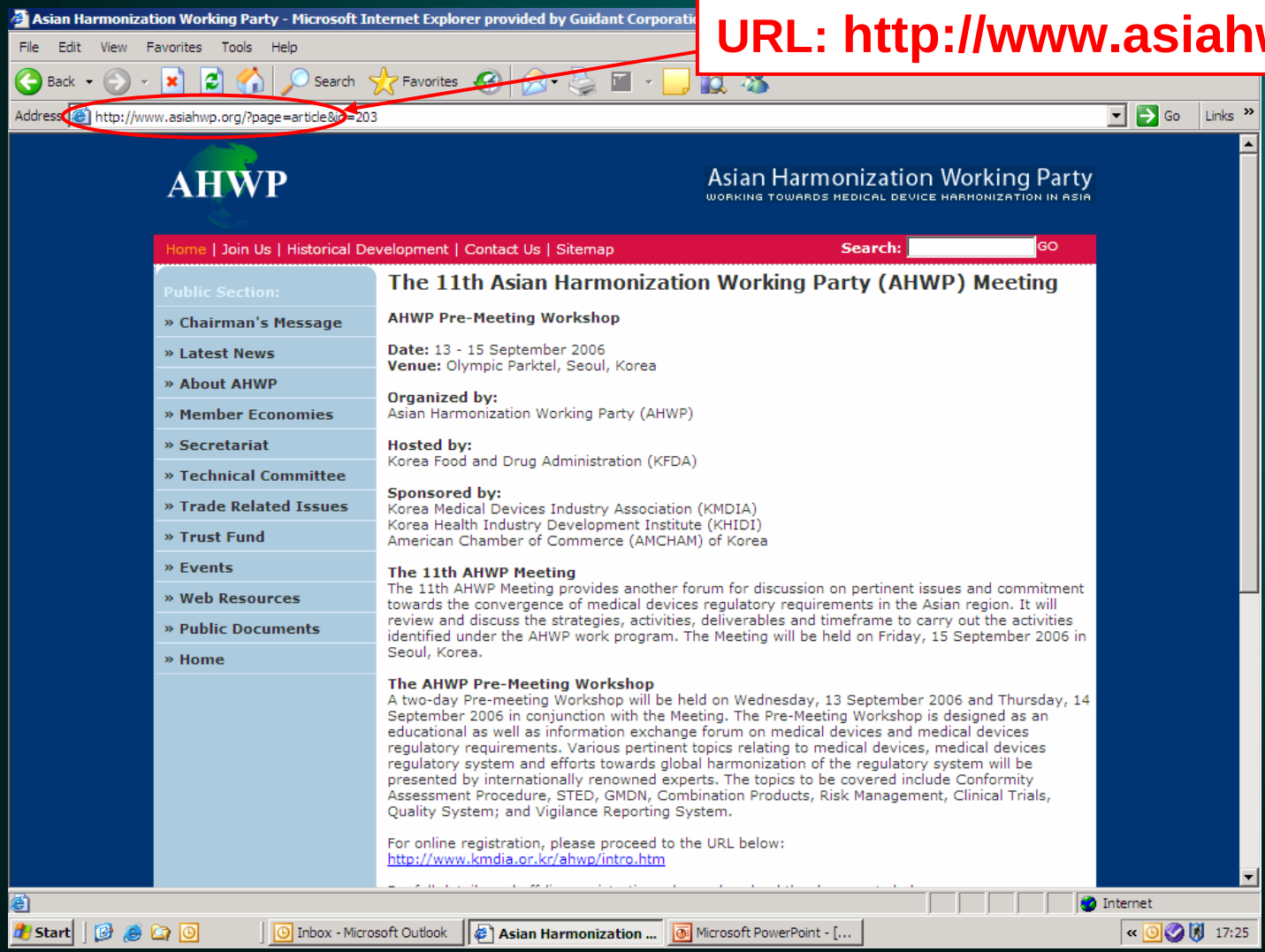
Asian Harmonization Working Party (AHWP)

Work program for 2005-2007

- Comparative study on existing medical device regulations in AHWP member economies
- Harmonization of definition, classification and nomenclature within AHWP
- Formalization of a post-marketing alert system
- Capacity building through training
- Work toward common submission dossier in alignment with ASEAN ACCSQ MDPWG
- Funding

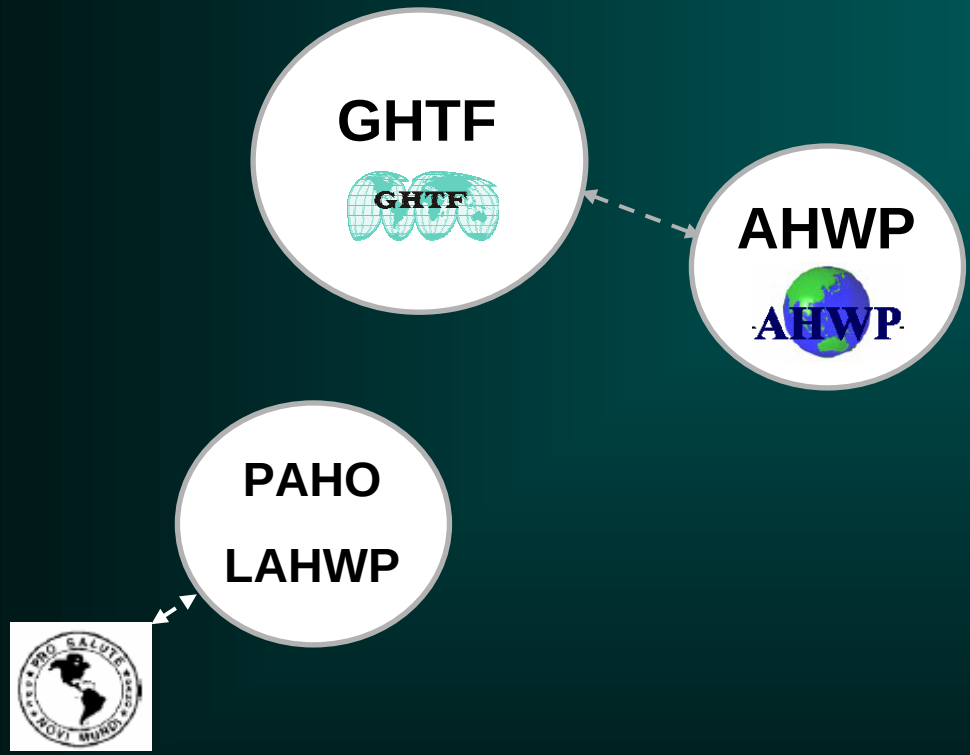
Asian Harmonization Working Party (AHWP)

URL: http://www.asiahwp.org/



Source: APEC

Asia-Pacific medical device regional regulatory harmonization initiatives



Pan American Health Organization

"RESOLVES:

2. To support the proposal to form an ad hoc group to promote and facilitate the medical devices harmonization processes in the Americas.

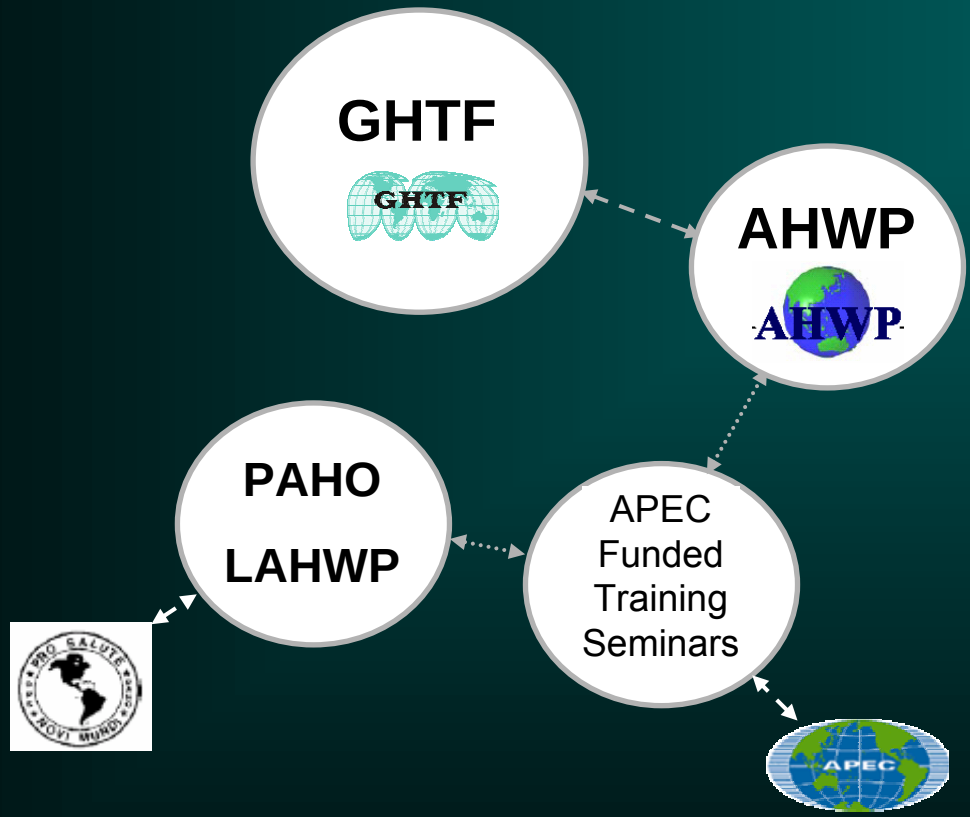
3. To urge the Member States to:

(a) develop and strengthen their programs for the regulation of medical devices;

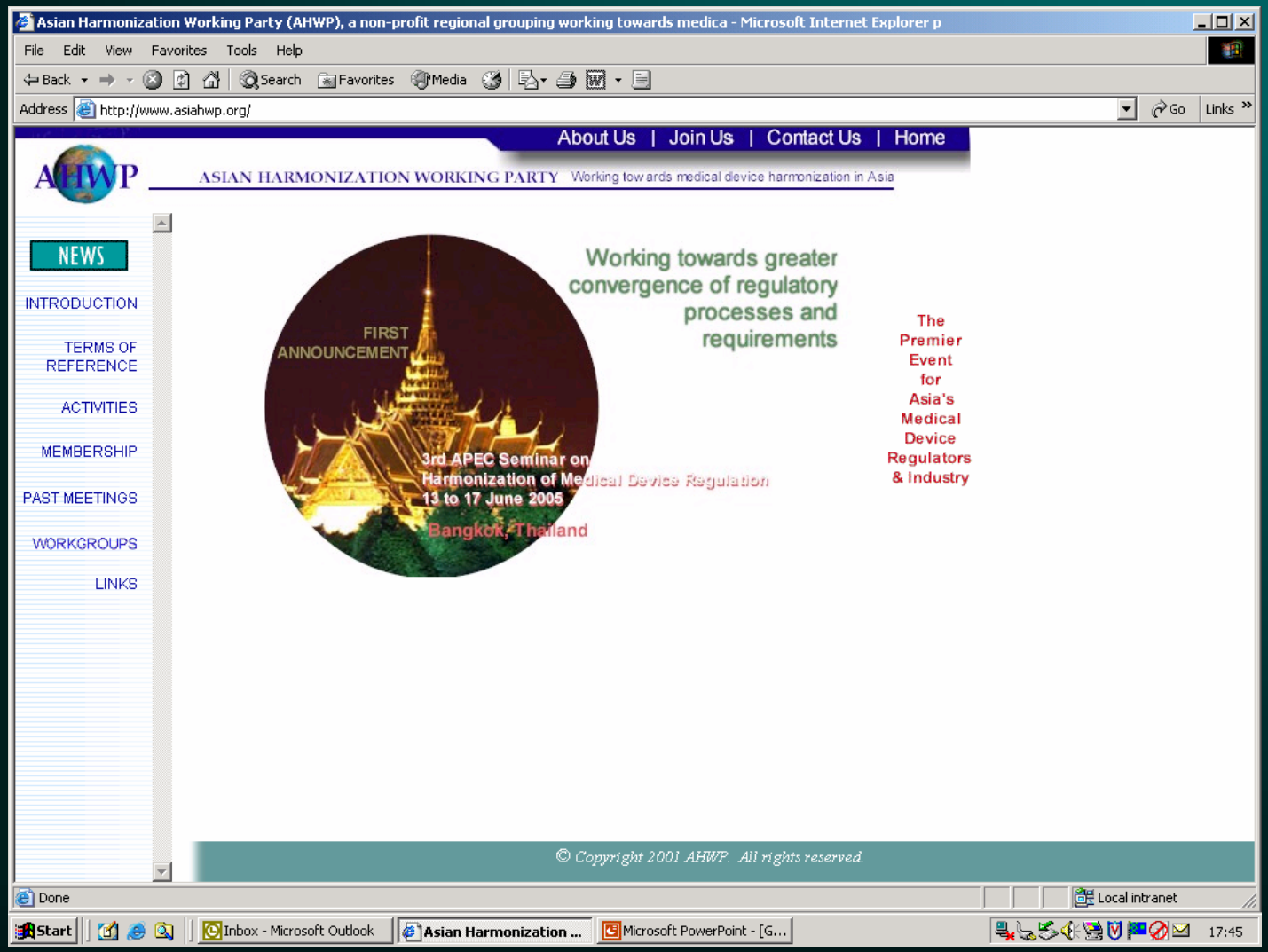
(b) promote and support the participation of their regulatory authorities at the general meetings of the Global Harmonization Task Force (GHTF) and those of its four study groups, while promoting the use of GHTF documents in their programs for the regulation of medical devices."

Source: Pan American Health Organization: 42nd Directing Council, 28 Sept. 2000 Provisional Summary Record of the Eighth Meeting

Asia-Pacific medical device regional regulatory harmonization initiatives

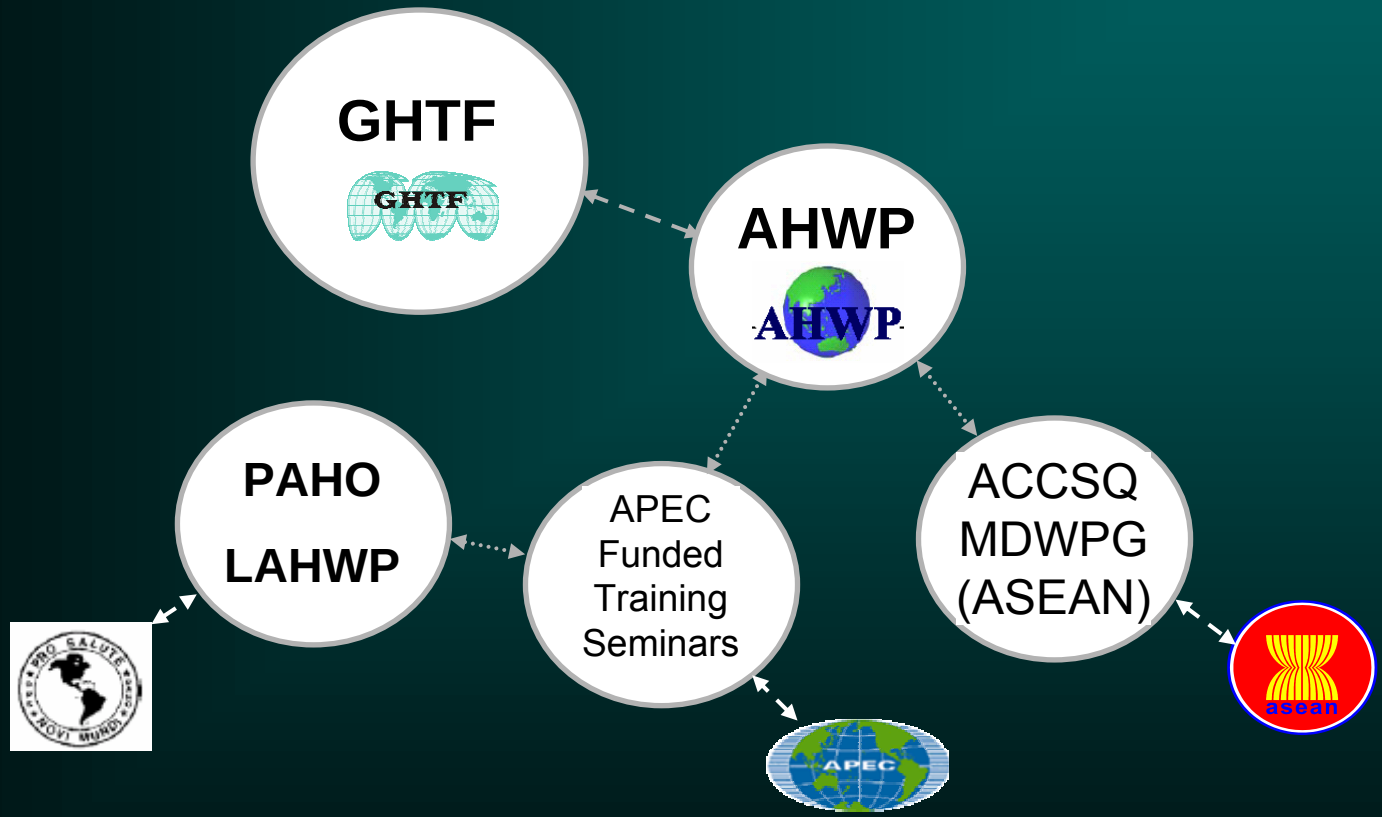


APEC funded regional regulatory training

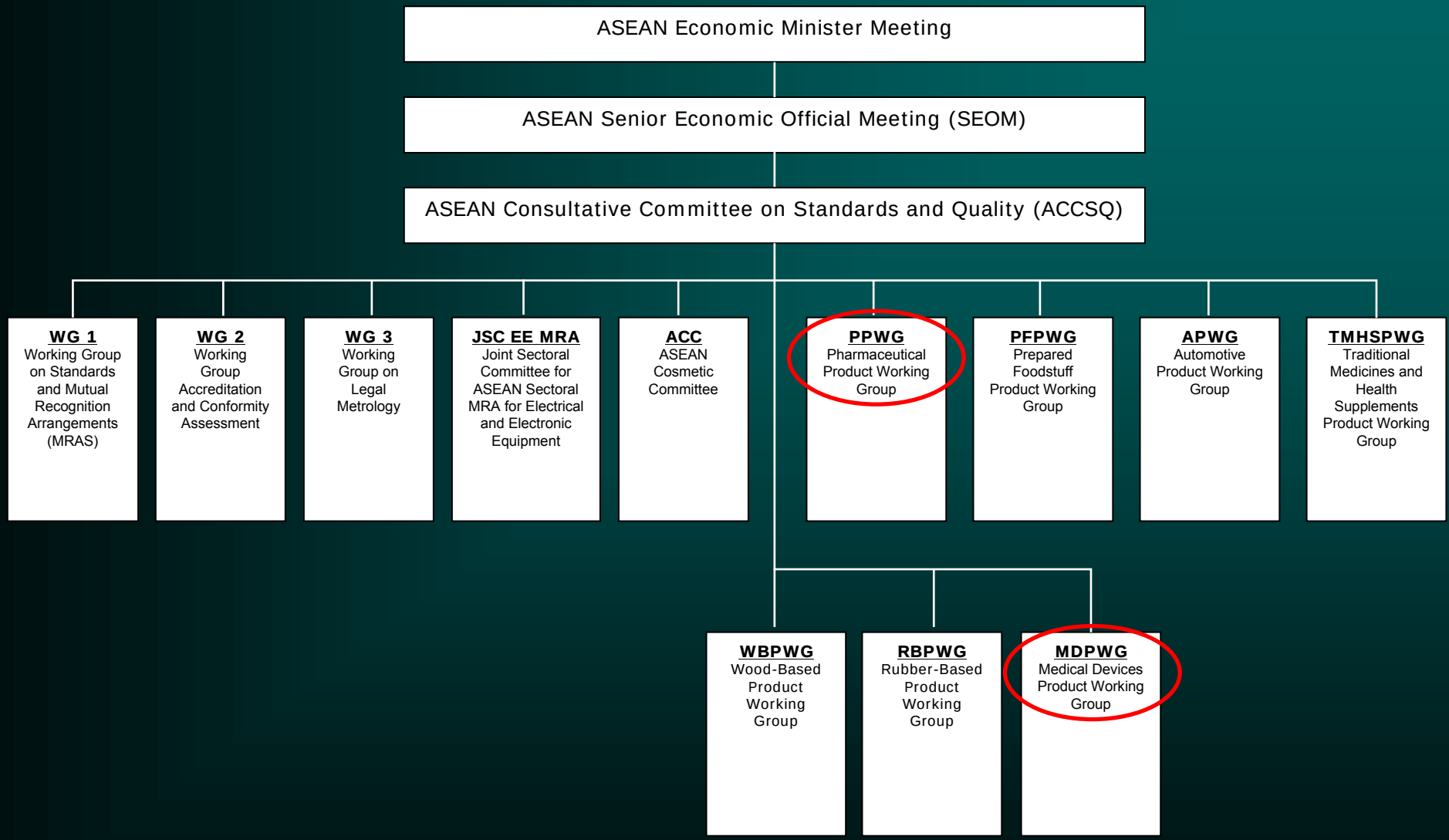


APEC funded regional regulatory training

Asia-Pacific medical device regional regulatory harmonization initiatives



ASEAN ACCSQ MDPWG



ASEAN Consultative Committee on Standards and Quality Medical Devices Product Working Group

- Mandate from ministers to remove technical barriers to trade, to provide medical industry in ASEAN with a better environment for growth, and to ensure faster access to safe and effective medical devices
- Emphasis on need to coordinate with GHTF and align regional regulatory framework with international practices
- ASEAN objective to promote harmonization of standards
- Accelerating economic integration toward establishment of Asian economic community

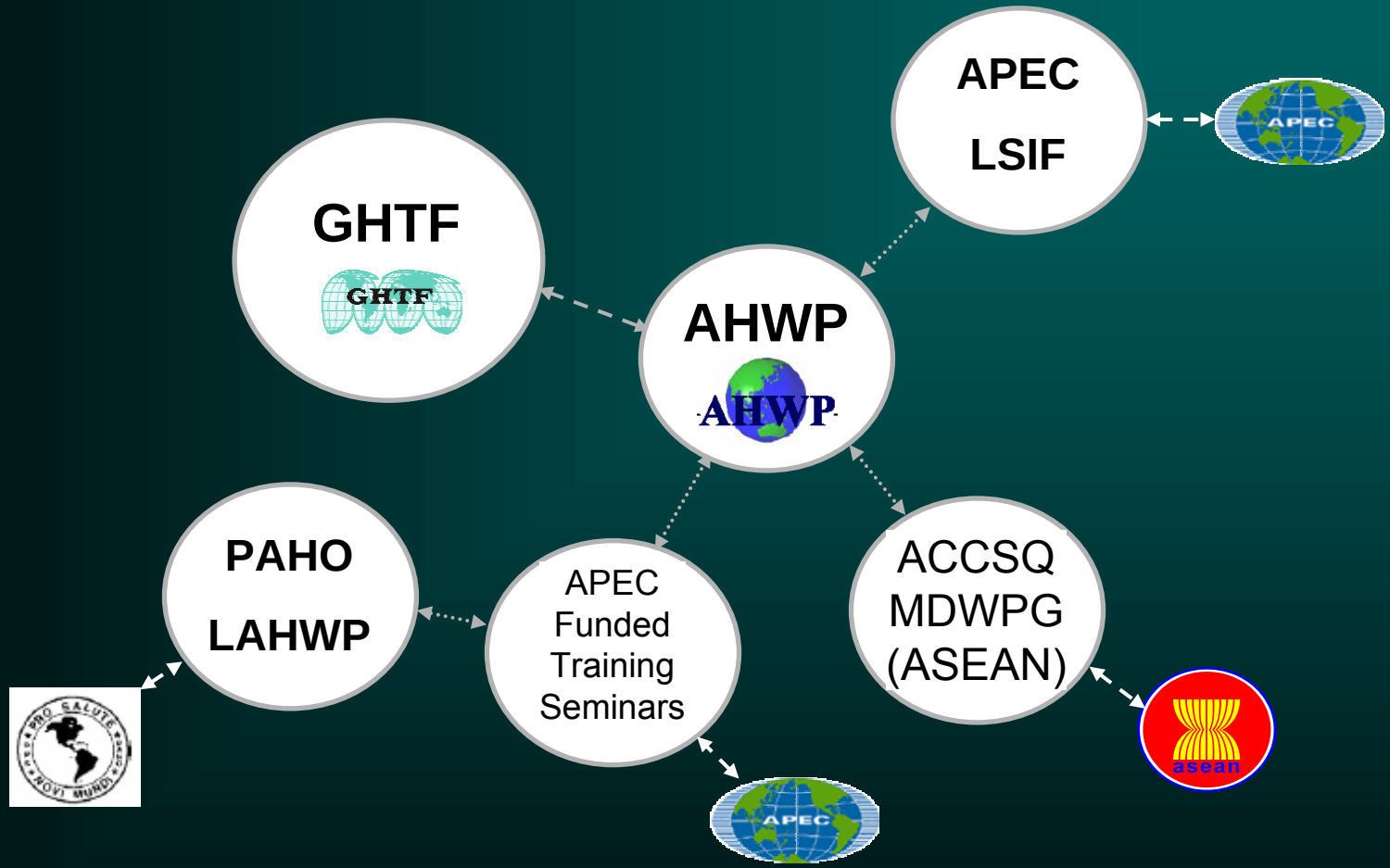
ASEAN Consultative Committee on Standards and Quality Medical Devices Product Working Group

- Chair: Malaysia; Co-Chair: Singapore
- Scope of activities:
  - Developing a common submission dossier template for product approval in ASEAN
  - Explore feasibility of abridged approval process for devices which regulators of benchmarked countries or recognized regulators have approved
  - Explore feasibility of adopting harmonized system of placement of medical devices into ASEAN markets, based on common approval process

ASEAN Consultative Committee on Standards and Quality Medical Devices Product Working Group

- Scope of activities (cont'd):
  - Formalize a post-marketing alert system for defective or unsafe medical devices
  - All ASEAN countries to consider joining AHWP and work in parallel with GHTF on technical harmonization efforts
- Industry invited to participate as observers
- Most recent meeting 14-16 Feb. 2006, Chiang Mai, Thailand

Asia-Pacific medical device regional regulatory harmonization initiatives



APEC Life Sciences Innovation Forum

"Life Sciences innovation was recognised as a critical area of growth and socio-economic development - healthy people produce healthy economies. Productivity gains far outweigh the costs of developing innovative products. New product development and use adds significantly to longevity, wellness and economic potential.

Successful Life Sciences industry requires political leadership and commitment from the top and depends on the proper policy environment, public-private partnership, human capacity, and efficient and effective delivery of patient focused products and services. …

Source: APEC Life Sciences Innovation Forum: http://www.apec.org/apec/apec_groups/other_apec_groups/life_sciences.html

APEC Life Sciences Innovation Forum

"Capacity building for the harmonization of standards and regulatory practices for bio-medical products and services according to international best practices where the need is most pressing and obstacles are the greatest."

Source: APEC Life Sciences Innovation Forum: http://www.apec.org/apec/apec_groups/other_apec_groups/life_sciences.html

Conclusions

- Regional and international regulatory harmonization supports global medical device product development and clinical trial strategies
- Regional harmonization initiatives underway
  - Opportunity for prospective harmonization
  - Need sustained political support and funding
  - Coordination would be helpful
- Initiatives can promote timely access of patients, clinicians, and health care systems to safe and effective medical device technology

GHTF Vision

Enhancing the health of the public worldwide and facilitating innovation by harmonizing the global regulatory environment

APEC funded regional regulatory training – Bangkok, 13-17 June 2005

- 201 regulators and industry representatives
  - 13 economies with developing regulatory systems
  - 15 APEC economies
  - 6 non-APEC economies
  - Regulators from APEC economies with developing regulatory systems: 69
  - Industry representatives from APEC economies with developing regulatory systems: 104
  - Others (trainers, etc.): 28

How can APEC LSIF help these regional medical device regulatory harmonization initiatives?

In view of the emerging public health and population challenges,

In view of the regional objectives of promoting capacity building for medical device regulators,

In view of the industrial development policies of national governments and regional cooperative bodies, and …

How can APEC LSIF help these regional medical device regulatory harmonization initiatives?

In view of the APEC LSIF objective of capacity building for harmonization of standards and regulatory practices for biomedical products according to international best practices where the need is most pressing and obstacles are greatest ….

How can APEC LSIF help these regional medical device regulatory harmonization initiatives?

Recommend to Ministers to promote the adoption of GHTF guidance documents in APEC member economies

- consistent with local public health priorities
- in stages, from basic regulatory controls to more advanced and intensive controls as resources permit
- consider regional “pooling of competence” in conformity assessment

How can APEC LSIF help these regional medical device regulatory harmonization initiatives?

Recommend to Ministers to promote closer coordination between regional medical device regulatory harmonization initiatives

How can APEC LSIF help these regional medical device regulatory harmonization initiatives?

APEC funding and institutional support mechanisms should be considered in support of:

- Funding to continue and expand ACCSQ-MDWPG comparative study on medical device control in ASEAN member countries
- Financial support for ongoing work of AHWP and LAHWP
- Development and maintenance of expanded AHWP, ACCSQ-MDWPG, and LAHWP websites

How can APEC LSIF help these regional medical device regulatory harmonization initiatives?

APEC funding and institutional support mechanisms should be considered in support of (cont'd):

- More frequent regional training seminars, with greater numbers of participants from national regulatory authorities
- Development of "E-learning" tools
- Training for regulators on specific technologies
- Establishment of a "dense regulatory knowledge network" at regional levels

How can APEC LSIF help these regional medical device regulatory harmonization initiatives?

APEC funding and institutional support mechanisms should be considered in support of (cont'd):

- Collaborative development and promulgation of regional guidelines based on GHTF guidance documents and GMDN
- Support of pilot projects, e.g., evaluation of harmonized premarket conformity assessment dossier formats
- Promotion of adoption and recognition of international standards (ISO, IEC) without national deviations

How can APEC LSIF help these regional medical device regulatory harmonization initiatives?

APEC funding and institutional support mechanisms should be considered in support of (cont'd):

- Establishment and maintenance of regional Internet-based database and information exchange network for medical device adverse event/vigilance reports
- Pilot studies of regional mutual acceptance of results of premarket conformity assessments and/or results of regulatory audits